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The impact of buprenorphine and methadone on mortality: a primary care cohort study in the United Kingdom

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ABSTRACT

Aims To estimate whether opioid substitution treatment (OST) with buprenorphine or methadone is associated with a greater reduction in the risk of all-cause mortality (ACM) and opioid drug-related poisoning (DRP) mortality. **Design** Cohort study with linkage between clinical records from Clinical Practice Research Datalink and mortality register. **Setting** UK primary care. **Participants** A total of 11 033 opioid-dependent patients who received OST from 1998 to 2014, followed-up for 30 410 person-years. **Measurements** Exposure to methadone (17 373, 61%) OST episodes or buprenorphine (9173, 39%) OST episodes. ACM was available for all patients; information on cause of death and DRP was available for 5935 patients (54%) followed-up for 16 363 person-years. Poisson regression modelled mortality by treatment period with an interaction between OST type and treatment period (first 4 weeks on OST, rest of time off OST, first 4 weeks off OST, rest of time out of OST censored at 12 months) to test whether ACM or DRP differed between methadone and buprenorphine. Inverse probability weights were included to adjust for confounding and balance characteristics of patients prescribed methadone or buprenorphine. **Findings** ACM and DRP rates were 1.93 and 0.53 per 100 person-years, respectively. DRP was elevated during the first 4 weeks of OST [incidence rate ratio (IRR) = 1.93 95% confidence interval (CI) = 0.97–3.82], the first 4 weeks off OST (IRR = 8.15, 95% CI = 5.45–12.19) and the rest of time out of OST (IRR = 2.13, 95% CI = 1.47–3.09) compared with mortality risk from 4 weeks to end of treatment. Patients on buprenorphine compared with methadone had lower ACM rates in each treatment period. After adjustment, there was evidence of a lower DRP risk for patients on buprenorphine compared with methadone at treatment initiation (IRR = 0.08, 95% CI = 0.01–0.48) and rest of time on treatment (IRR = 0.37, 95% CI = 0.17–0.79). Treatment duration (mean and median) was shorter on buprenorphine than methadone (173 and 40 versus 363 and 111, respectively). Model estimates suggest that there was a low probability that methadone or buprenorphine reduced the number of DRP in the population: 28 and 21%, respectively. **Conclusions** In UK general medical practice, opioid substitution treatment with buprenorphine is associated with a lower risk of all-cause and drug-related poisoning mortality than methadone. In the population, buprenorphine is unlikely to give greater overall protection because of the relatively shorter duration of treatment.

Keywords Buprenorphine, drug related deaths, methadone, mortality, opioids, opioid substitution treatment, treatment cohort.

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INTRODUCTION

People with opioid dependence have more than 10 times the risk of premature mortality than the general population, and often cycle in and out of drug treatment before achieving stable remission and cessation of opioid use [1–6]. Methadone and buprenorphine are effective and essential medicines for the management of opioid dependence [7,8]. Opioid substitution treatment (OST) has positive benefits across multiple outcomes on mortality risk,

transmission of HIV and hepatitis C virus (HCV), HIV treatment prognosis and drug-related crime [1,9–16]. OST is highly cost-effective, whether delivered in the community or prison [17–19]. Prolonged OST is associated with improved survival [5]; however, recent studies highlight very high mortality risk in the month after treatment cessation [20–23]. There have also been reports of an elevated risk of mortality during the first month of OST [20,21,24,25].

Buprenorphine became available in the United Kingdom in 1998 and OST has expanded more than fivefold since 2000 [26]. However, trends in the overall number of drug and opioid-related deaths continue to rise, with the highest number ever recorded at more than 1200 deaths in 2015/16 [27]. In the United States, more than 60 000 people died from an overdose in 2016: a fourfold increase in the last 15 years [28]. While methadone is a full mu-opioid agonist, buprenorphine is a partial mu-opioid agonist, providing a 'ceiling effect' for respiratory depression and potentially limiting the effect of additional heroin use [29,30]. Qualitative studies in the United States suggest that patient preference for buprenorphine and methadone varies, and is influenced by peer attitudes, prior treatment experience and clinic dispensing practices [31–33]. Internationally, there is no consensus about which medication to use. In the United Kingdom, methadone is recommended as the first-line treatment if there are no contraindications [8].

In a recent US randomized controlled trial, patients with opioid dependence who received buprenorphine had a shorter duration of treatment and were more likely to drop out than those receiving methadone [34]. This association has been reported by systematic reviews [19,35]. A recent Australian cohort study of OST patients reported that the risk of death during the first 4 weeks was lower for buprenorphine compared to methadone—with no marked differences in mortality risk thereafter [24]—but with a shorter duration of treatment for patients on buprenorphine compared to methadone [21,36,37].

In the present study we examine relative mortality risk for patients with opioid dependence in primary care who receive buprenorphine or methadone. Our hypothesis was that buprenorphine is associated with a reduced mortality risk during OST, especially during the first 4 weeks of OST, and fewer opioid drug-related poisoning (DRP) deaths in the population.

METHODS

Study setting and databases

The study setting was general practitioner (GP) primary care practices in the United Kingdom reporting to the Clinical Practice Research Datalink (CPRD https://www.cprd.com/home/) (ISAC CPRD Protocol 14_073R2). The CPRD contains anonymized patient records from 674 GP practices and more than 11 million patients (some 7% of the UK population). CPRD is representative in terms of socio-demographic characteristics and has good validity and replicability in relation to chronic illness [38–40]. Linked cause-specific mortality data from the Office for National Statistics (ONS) are available on more than half the records only for GP practices (395) in England [38].

Patient cohort and OST exposure

We constructed a UK cohort from an extract of CPRD for 49 279 patients who received one or more prescriptions of methadone or buprenorphine between 1 January 1998 and 31 July 2014 (Fig. 1). Treatment episodes were periods of continuous prescription. If there was a gap of at least 28 days between the expected completion of one prescription and the start of the next, this was categorized as a new treatment episode [20].

Using diagnostic and prescription formulation information, we excluded 26 324 patients who were prescribed buprenorphine or methadone for pain relief, as well as 9950 patients who received doses below the minimum expected for OST (i.e. $<$ 20 mg/day methadone or $<$ 4 mg/day buprenorphine). Patients outside the 15–64-year age range were also dropped and all OST episodes involving both methadone and buprenorphine within a single OST episode to allow generation of propensity scores. In total, 606 GP practices had at least one patient on OST with information on all deaths. The final risk set yielded 11 033 patients followed-up for 30 410 person-years over 26 546 episodes and 512 581 prescriptions, with an average duration of 14 days; 17 373 (61%) OST episodes were methadone and 9173 (39%) OST episodes were buprenorphine.

Linkage to information on cause of death was available for 5935 patients (54%) followed-up for 16 363 person-years, comprising 9550 (61%) OST episodes on methadone and 6050 (39%) on buprenorphine.

We estimated treatment duration from completed episodes and imputing for patients still in OST at the end of follow-up based on averaging 100 predictions from the log-normal distributions estimated by a parametric survival analysis.

Outcome measures

All-cause mortality (ACM) was derived from dates of death recorded within CPRD and DRP classified from the underlying cause of death (Supporting information, Table S1) [27,41,42].

Statistical analyses

Each OST episode was modelled as four periods of exposure [20,24,43]: weeks 1–4 on OST, rest of time on OST,

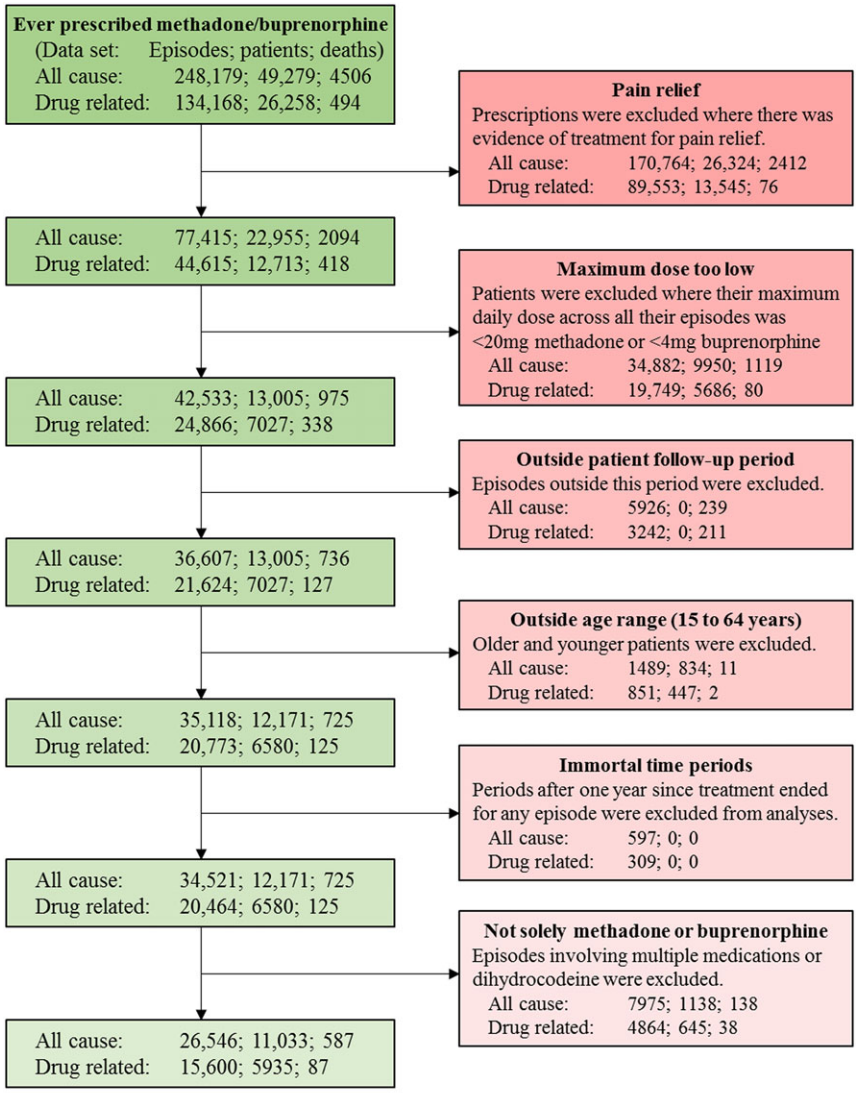

Figure 1 Flow diagram of clinical practice research datalink extract and cohort risk set for analysis: patients prescribed methadone or buprenorphine 1998–July 2014 for opioid substitution treatment (OST). The above figure shows numbers of episodes, patients and deaths for the all-cause and drug-related data sets. Identification of prescriptions for pain relief were based upon prescription text, medication in the form of patches or episodes of dihydrocodeine prior to starting OST. The follow-up period varied by patient and reflected a combination of the study period (January 1998–July 2014), the patient registration period with the primary care practice, the Clinical Practice Research Datalink (CPRD) usable data date and 1 year after the last treatment ended. The exclusion of periods greater than 1 year after the cessation of treatment for each episode (immortal time bias) affected the person-years at risk, but not the number of deaths [Colour figure can be viewed at wileyonlinelibrary.com]

weeks 1–4 off OST and rest of time off OST censored at 12 months after each treatment episode. This censoring avoided cumulative dilution of mortality risks by excluding periods where patients may have ceased opioid use and minimized immortal time bias. Mortality incidence rate ratios (IRRs) of ACM or DRP were estimated using Poisson regression. We first fitted models with a random effect of GP practice. However, with minimal evidence of clustering [variance by practice = 0.2, 95% confidence interval (CI) = 0.1–0.5] we judged it appropriate to conduct the analysis without including clustering at practice level. The main hypothesis was tested by fitting an interaction between OST modality and treatment period. IRRs are reported relative to methadone for each treatment period.

Confounding

We first adjusted for sex, age, calendar year, comorbidity score and geographical region following earlier analyses [20,21,44,45]. Comorbidity was calculated based upon 17 chronic illnesses and their associated weights, as defined by Khan *et al.* [46], and was incorporated as a time-varying score (0, 1, 2 or more).

Several characteristics were also included that could influence mortality risk: (a) benzodiazepine co-prescription;

(b) gabapentoid co-prescription; (c) number of OST patients per GP practice; (d) number of GPs prescribing per practice; and (e) history recorded of self-harm, overdose poisoning, alcohol problems, imprisonment or homelessness. We generated propensity scores (see Supporting information, Appendix S1) on the probability of being prescribed buprenorphine and incorporated these as inverse probability weight (IPW) into regression models to balance the covariates between the two OST medication groups and improve model stability [47]. An extended analysis using matched propensity scores could only be undertaken for ACM [47] (Supporting information, Appendix S1).

We observed a difference in mortality risk by age and comorbidity for patients prescribed methadone or buprenorphine and so included an interaction between OST modality and age and comorbidity in the final adjusted models.

Sensitivity analyses

We undertook a series of sensitivity analyses, as follows.

1 In the United Kingdom, OST is delivered in the community by primary care and community drug agencies often managed by third-sector providers. We tested that treatment duration on methadone and buprenorphine was similar for patients treated in primary care or through third-sector service providers.
2 We tested whether the differences in the pattern mortality risk by period for patients on buprenorphine and methadone persisted for patients and OST episodes without comorbidity.
3 We compared Poisson regression with negative binomial regression to account for overdispersion in the results.
4 We tested whether the findings changed after adjustment for evidence of planned discharge (tapering OST prior to discharge/cessation).

Other sensitivity analyses not reported below (Tables available on request) include: (5) addressing immortal time bias by dropping all episodes that began before patients were transferred into CPRD or follow-up began or including only the last treatment episode (no change in results) [48]; and testing that the direction and magnitude of IRR between buprenorphine and methadone were robust to changing the minimum gap between episodes (e.g. moving from fewer than 28 days to 7 days) (they were).

Effect of OST on DRP mortality in the population (Supporting information, Appendix S2)

We estimated the probability that OST reduces DRP in the population by calculating weighted mortality risk ratios (wMRR) of DRP deaths. wMRR compare the observed mortality risk in patients undergoing OST to assumed mortality risk of opioid-dependent patients who do not enter OST (accounting for fluctuating mortality risk in different periods on and off OST, and for variation in the duration of current treatment). We also estimate the minimum median duration of methadone and buprenorphine required to reduce DRP deaths in the population (Supporting information, Appendix S2).

RESULTS

Patient and OST characteristics

Table 1 shows patient, OST episode and practice characteristics. The proportion of buprenorphine episodes increased from < 20% in 1998–2000 to 41% in 2010–14. Mean (and median) duration of episodes was 363 (111) days and 173 [40] days for methadone and buprenorphine, respectively. The mean [standard deviation (SD)] dose for methadone was 65.3 mg/day (66.1) and 7.5 mg/day (9.2) for buprenorphine; 43% of methadone and 21% of buprenorphine episodes met the recommended therapeutic daily dose of ≥ 60 mg and ≥ 12 mg, respectively [49].

Approximately 15% of all OST episodes and fewer than 10% of OST episodes lasting less than 2 months showed evidence of a tapering dose towards a planned discharge from treatment. The mean number of OST episodes was 2.4. Sixty per cent of patients had OST episodes with only methadone, and 10% had at least one buprenorphine and one methadone OST episode.

Mortality

There were 587 deaths during OST or within 12 months of treatment cessation, giving an overall mortality rate of 1.93 deaths per 100 person-years. There were 87 DRPs, giving an overall mortality rate of 0.53 deaths per 100 person-years. Table 2 shows the ACM rates, DRP rates and unadjusted and adjusted IRRs by OST period and modality.

Confounders and propensity scores

Buprenorphine prescription varied by region, calendar period and practice size (Supporting information, Table S2). Women, older and more comorbid patients and patients co-prescribed gabapentoids were more likely to be prescribed buprenorphine. Patients co-prescribed benzodiazepines and with a reported history of self-harm, overdose, alcohol problems, imprisonment and homelessness were more likely to be prescribed methadone. Supporting information, Table S2 shows that IPW provided a better balance of covariates (towards 50 : 50) between patients treated with buprenorphine or methadone.

Table 1 Patient, opioid substitution treatment (OST) episode and practice characteristics.

		No. (%)	
Characteristic	*Category*	*Total*	*Linked to DRP records*[c]
Patients		11 033 (100.00)	5935 (100.00)
Gender	Female	3570 (32.36)	1851 (31.19)
Age (years) (on entry)	< 30	3468 (31.43)	1876 (31.61)
	30–39	4425 (40.11)	2409 (40.59)
	40–49	2020 (18.31)	1124 (18.94)
	50+	1120 (10.15)	526 (8.86)
Comorbidity score	0	7619 (69.06)	4178 (70.40)
(at exit from study)	1	2454 (22.24)	1409 (23.74)
	2+	960 (8.70)	348 (5.86)
OST medication	Methadone	7633 (69.18)	3745 (63.10)
	Buprenorphine	2619 (23.74)	1656 (27.90)
	Both	781 (7.08)	534 (9.00)
Benzodiazepines	Yes	4853 (43.99)	2430 (40.94)
Gabapentin/pregabalin	Yes	901 (8.17)	426 (7.18)
Self-harm history	Yes	209 (1.89)	87 (1.47)
Overdose history	Yes	2449 (22.20)	1381 (23.27)
Alcohol problems	Yes	2048 (18.56)	1068 (17.99)
Prison history	Yes	663 (6.01)	335 (5.64)
Homeless history	Yes	260 (2.36)	131 (2.21)
OST episodes		26 546 (100.00)	15 600 (100.00)
Methadone	All episodes	17 373 (65.44)	9550 (61.22)
By duration	Up to 1 month	4915 (28.29)	2923 (30.61)
	1–< 3 months	3157 (18.17)	1828 (19.14)
	3–< 6 months	2443 (14.06)	1381 (14.46)
	6–< 12 months	2298 (13.23)	1213 (12.70)
	12 months or longer	4560 (26.25)	2205 (23.09)
Buprenorphine	All episodes	9173 (34.56)	6050 (38.78)
By duration	Up to 1 month	4128 (45.00)	2704 (44.69)
	1–< 3 months	2007 (21.88)	1329 (21.97)
	3–< 6 months	1109 (12.09)	755 (12.48)
	6–< 12 months	826 (9.00)	556 (9.19)
	12 months or longer	1103 (12.02)	706 (11.67)
By year of initiation	1998–2000	2726 (83.20)	1434 (84.73)
(% methadone)	2000–2004	8730 (69.53)	4750 (64.99)
	2005–2009	9157 (60.43)	5583 (56.67)
	2010–2014	5933 (59.01)	3833 (54.37)
Completed/uncensored		23 685 (89.22)	14 234 (91.24)
Planned discharge[a]	< 2 months	945 (7.94)	588 (7.93)
(by duration)	2+ months	2596 (22.02)	1472 (21.60)
Methadone	All completed	15 117 (63.83)	8550 (89.53)
Maximum dose	≥ 60 mg per day	6539 (43.26)	3210 (37.54)
Buprenorphine	All completed	8568 (36.17)	5684 (93.95)
Maximum dose	≥ 12 mg per day	1833 (21.39)	1271 (22.36)
GP practices		606 (100.00)	352 (100.00)
OST patients[b]	1–2	285 (47.03)	162 (46.02)
	3–9	227 (37.46)	132 (37.50)
	10+	94 (15.51)	58 (16.48)
Prescribing GPs[b]	1–4	135 (22.28)	67 (19.03)
	5–9	261 (43.07)	141 (40.06)
	10+	210 (34.65)	144 (40.91)
Region	North East	11 (1.82)	9 (2.56)
	North West	74 (12.21)	58 (16.48)
	Yorkshire/Humber	29 (4.79)	17 (4.83)

(***Continues***)

Table 1. (Continued)

Characteristic	*Category*	*No. (%)*	
		Total	*Linked to DRP records*[c]
	East Midlands	23 (3.80)	12 (3.41)
	West Midlands	49 (8.09)	37 (10.51)
	East	50 (8.25)	37 (10.51)
	South West	56 (9.24)	46 (13.07)
	South Central	48 (7.92)	35 (9.94)
	London	73 (12.05)	56 (15.91)
	South East	57 (9.41)	45 (12.78)
	Northern Ireland	19 (3.14)	
	Scotland	71 (11.72)	
	Wales	46 (7.59)	

[a]Evidence of a decrease in dose over last 28 days of OST—shown separately for episodes with < 2 months (11 897 total and 7418 linked episodes) and 2+ months duration (11 788 total and 6816 linked episodes). [b]Average for each practice derived from 5802 practice years. [c]Linked to Office for National Statistics (ONS) mortality register for information on drug-related poisonings (DRP). GP = general practitioner.

Mortality by treatment period

Table 2 shows that ACM and DRP vary considerably by treatment period. At the lowest risk period from 4 weeks on OST until treatment cessation the ACM and DRP mortality rates were 0.98 and 0.29 per 100 person-years, respectively. Compared to being on OST during that period (our referent) the ACM risk was more than three times (95% CI = 2.31–4.36) higher during the first 4 weeks of treatment, nearly 10 times (95% CI = 7.87–12.01) higher during the first 4 weeks after treatment ceased and more than two times higher (95% CI = 1.82–2.73) in the rest of the period out of treatment. Adjustment for sex, age, year, comorbidity, region and OST modality or using IPW did not alter these findings.

The IRR for DRP mortality risk was 3.03 (95% CI = 1.37–6.66), 5.85 (95% CI = 3.22–10.63) and 2.20 (95% CI = 1.32–3.64) for the first 4 weeks on OST, the first 4 weeks off OST and the rest of time off treatment, respectively, compared to being on OST from 4 weeks to end of treatment. After adjustment using IPW and other interactions (between OST modality and age and comorbidity) the DRP mortality risk in the first 4 weeks on OST reduced slightly (IRR = 1.93, 95% CI = 0.97–3.82) and the mortality risk during the first 4 weeks after treatment ceased increased slightly (IRR = 8.15, 95% CI = 5.45–12.19) compared to the rest of time on OST.

Buprenorphine compared to methadone

Patients on buprenorphine compared to methadone had a lower all-cause mortality (ACM) rate in each treatment period. Adjusting for sex, age, year, comorbidity and region or using IPW or matching on propensity score tended to strengthen the difference in ACM risk between buprenorphine and methadone (Fig. 2).

DRP during the first 4 weeks of OST was 1.24 per 100 person-years for patients on methadone compared to 0.30 per 100 person-years for patients on buprenorphine (Table 2). After adjustment (Fig. 2), incorporating IPW and interactions between OST modality and age and comorbidity, evidence strengthened for a difference in DRP for patients on buprenorphine compared to methadone. Patients on buprenorphine had a lower risk of DRP during the first 4 weeks of treatment (IRR = 0.08, 95% CI = 0.01–0.48), as well as the rest of time on OST (IRR = 0.37, 95% CI = 0.17–0.79) compared to patients on methadone. There was no evidence for a difference in mortality risk for patients on buprenorphine compared to methadone during the first 4 weeks after treatment ceased, but a larger difference in the period after the first 4 weeks post-treatment to 12 months after termination of OST (IRR = 0.23, 95% CI = 0.12–0.48).

Age and comorbidity

Table 3 shows evidence for interactions between age and comorbidity with OST modality. ACM, but not DRP, increased with age. For both ACM and DRP the risk of mortality was lower in older patients prescribed buprenorphine compared to patients prescribed methadone.

Comorbidity was associated with both ACM and DRP and the risk of ACM and DRP was substantially lower for comorbid patients prescribed buprenorphine compared to methadone. The mortality risk was considerably higher (15.9 per 100 person-years) for people with two or more comorbidities, and 90% of the deaths in this group

Table 2 Adjusted and unadjusted analysis of association between opioid substitution treatment (OST) modality and treatment period and all-cause and drug-related mortality.

				Unadjusted			*Adjusted*[a]		*IPW adjusted*[a]		*IPW adjusted + interactions*[b]	
Period	*OST type*	*Deaths*	*PY*	*MR*	*IRR (95% CI)*	*P*	*IRR (95% CI)*	*P*	*IRR (95% CI)*	*P*	*IRR (95% CI)*	*P*
All-cause mortality												
On 1–4 weeks		48	1541	3.11	3.17 (2.31–4.36)	**< 0.0001**	3.25 (2.35 to 4.49)	**< 0.0001**	3.09 (2.53 to 3.77)	**< 0.0001**	2.98 (2.44 to 3.64)	**< 0.0001**
On rest		179	18 240	0.98	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Off 1–4 weeks		165	1730	9.54	9.72 (7.87–12.01)		10.37 (8.33 to 12.91)		10.51 (9.17 to 12.05)		10.40 (9.07 to 11.92)	
Off rest		195	8900	2.19	2.23 (1.82–2.73)		2.81 (2.28 to 3.46)		2.77 (2.42 to 3.16)		2.77 (2.42 to 3.17)	
On 1–4 weeks	Methadone	46	1036	4.44	1 (ref)	**0.0001**	1 (ref)	**0.0001**	1 (ref)	**< 0.0001**	1 (ref)	**< 0.0001**
	Buprenorphine	2	505	0.40	0.09 (0.02–0.37)	0.0008	0.04 (0.01 to 0.16)	< 0.0001	0.03 (0.01 to 0.08)	< 0.0001	0.04 (0.01 to 0.15)	< 0.0001
On rest	Methadone	157	14 639	1.07	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
(ref)	Buprenorphine	22	3601	0.61	0.57 (0.36–0.89)	0.0134	0.26 (0.16 to 0.41)	< 0.0001	0.30 (0.23 to 0.39)	< 0.0001	0.48 (0.35 to 0.64)	< 0.0001
Off 1–4 weeks	Methadone	150	1091	13.75	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
	Buprenorphine	15	639	2.35	0.17 (0.10–0.29)	< 0.0001	0.07 (0.04 to 0.11)	< 0.0001	0.09 (0.07 to 0.12)	< 0.0001	0.17 (0.12 to 0.24)	< 0.0001
Off rest	Methadone	153	6054	2.53	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
	Buprenorphine	42	2846	1.48	0.58 (0.42–0.82)	0.0020	0.21 (0.15 to 0.30)	< 0.0001	0.26 (0.21 to 0.32)	< 0.0001	0.41 (0.32 to 0.52)	< 0.0001
Drug-related poisoning												
On 1–4 weeks		8	897	0.89	3.03 (1.37–6.66)	**< 0.0001**	3.08 (1.38 to 6.83)	**< 0.0001**	1.87 (0.95 to 3.71)	**< 0.0001**	1.93 (0.97 to 3.82)	**< 0.0001**
On rest		27	9165	0.29	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Off 1–4 weeks		18	1044	1.72	5.85 (3.22–10.63)		5.97 (3.24 to 11.00)		7.84 (5.25 to 11.72)		8.15 (5.45 to 12.19)	
Off rest		34	5257	0.65	2.20 (1.32–3.64)		2.19 (1.30 to 3.68)		2.06 (1.42 to 2.99)		2.13 (1.47 to 3.09)	
On 1–4 weeks	Methadone	7	563	1.24	1 (ref)	**0.2944**	1 (ref)	**0.2531**	1 (ref)	**0.0136**	1 (ref)	**0.0069**
	Buprenorphine	1	334	0.30	0.24 (0.03–1.96)	0.1830	0.27 (0.03 to 2.17)	0.2162	0.17 (0.03 to 0.96)	0.0453	0.08 (0.01 to 0.48)	0.0057
On rest	Methadone	23	6924	0.33	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
(ref)	Buprenorphine	4	2242	0.18	0.54 (0.19–1.55)	0.2513	0.53 (0.18 to 1.54)	0.2430	0.74 (0.42 to 1.33)	0.3219	0.37 (0.17 to 0.79)	0.0105
Off 1–4 weeks	Methadone	10	620	1.61	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
	Buprenorphine	8	424	1.89	1.17 (0.46–2.97)	0.7400	1.32 (0.51 to 3.43)	0.5718	1.58 (0.87 to 2.89)	0.1321	0.78 (0.36 to 1.66)	0.5152
Off rest	Methadone	28	3379	0.83	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
	Buprenorphine	6	1878	0.32	0.39 (0.16–0.93)	0.0341	0.41 (0.17 to 1.01)	0.0524	0.53 (0.32 to 0.88)	0.0143	0.23 (0.12 to 0.48)	0.0001

PY = person-years follow-up (person-years at risk); MR = mortality rate (deaths/100 person-years); IRR incidence rate ratio; IPW = inverse probability weighting based upon propensity scores; CI = confidence interval. Main effect and interaction *P*-values (3 degrees of freedom) are shown in bold type. In the first panel for all-cause mortality (ACM) or drug-related poisoning (DRP) mortality risk is compared to period on OST from 4 weeks to end of OST (On rest). The likelihood ratio tests whether there is evidence of a difference in mortality risk by time-period. In the second panel mortality risk of patients on buprenorphine is compared to methadone in each time-period. [a]Adjusted for gender, age, year, comorbidity, region and, where applicable, treatment period and OST type. [b]Additionally adjusted for age × OST type and comorbidity × OST type interactions ratio. IRRs are averaged across age and comorbidity strata.

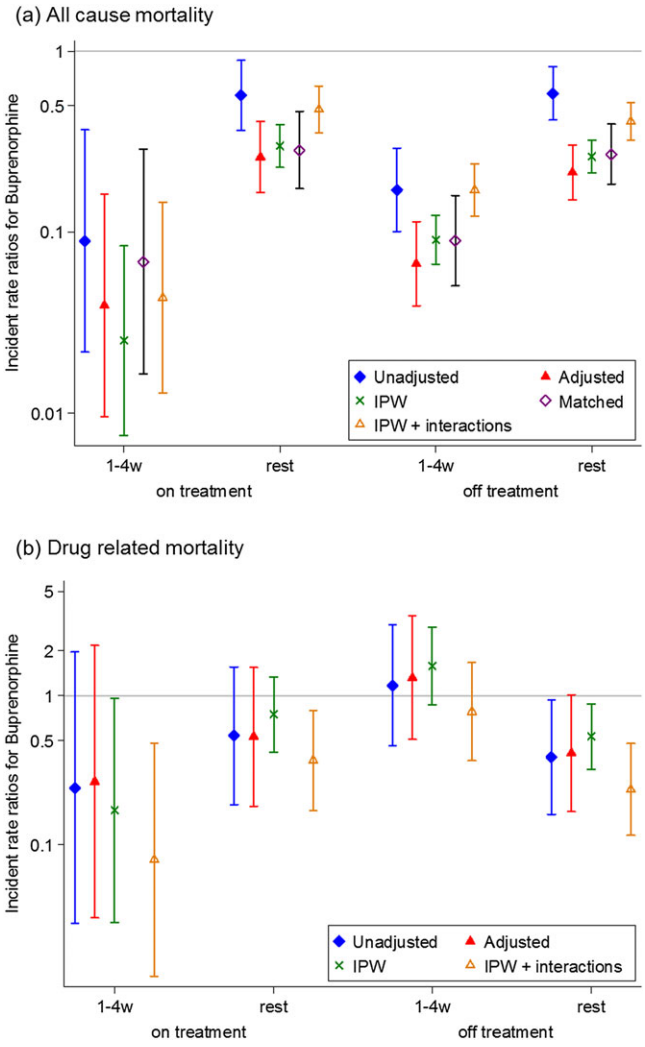

Figure 2 Comparison of adjusted incidence rate ratios (IRR) comparing mortality risk for patients on buprenorphine or methadone by period on and off treatment with and without propensity score weights and matching. The figure shows the risk of mortality for buprenorphine relative to methadone for the four treatment periods by all-cause a or drug related mortality b and by adjusted, propensity score based weighted analyses (IPW), propensity score-matched analyses and IPW analyses with additional adjustment for interactions of opioid substitution treatment (OST) with age or comorbidity. Incidence rate ratios are shown on a log scale with 95% confidence intervals. Results for matched episodes in drug-related mortality analyses are not shown due to the small number of deaths [Colour figure can be viewed at wileyonlinelibrary.com]

occurred in people who were currently or last treated on methadone.

Sensitivity analysis

Treatment duration for patients on buprenorphine and methadone is highly skewed (as shown in Table 1, Fig. 4 and Supporting information, Table S3). We found similar distributions in patients treated in primary care (our observed CPRD data set) and a leading third-sector provider of community drug treatment (Supporting information, Table S3).

Supporting information, Table S4 shows multiple sensitivity analyses. These showed that the differential patterns in mortality rates by the period on and off OST and between patients receiving methadone or buprenorphine remain for patients without comorbidity (i.e. when comorbid patients and episodes are excluded; see mortality rates in model B). There are also similar mortality rates if mixed OST episodes involving buprenorphine and methadone are included (model C). The final adjusted model shown in Table 2 (model A) is robust to additional adjustment for planned discharge (evidence of tapering dose prior to cessation, model D) and alternative regression models (negative binomial) that allow for overdispersion in the outcome (model E).

Expected impact of OST on DRP compared to no treatment

Figure 3 shows that there is insufficient evidence that OST reduces the number of DRP deaths in the population for patients on methadone or buprenorphine: weighted mortality rate ratio (wMRR) 1.55 (95% CI = 0.54–3.80) and 1.79 (95% CI = 0.48–5.24), respectively (see Supporting information, Appendix S2). We estimated the probability that methadone or buprenorphine reduces drug-related deaths in the population to be 28 and 21%, respectively. Modelling the impact of inducing all OST patients on buprenorphine then switching either 50 or 100% patients to methadone (given observed duration of treatment) improves the probability of benefit slightly, but it remains lower than 50%.

Table 3 All-cause mortality and drug-related poisoning mortality risk by age and comorbidity and their interaction with type of opioid substitution treatment (OST).

					Unadjusted		*Adjusted*[a]		*IPW adjusted*[a]	
	OST type	*Deaths*	*PY*	*MR*	*IRR (95% CI)*	*P*	*IRR (95% CI)*	*P*	*IRR (95% CI)*	*P*
Age × OST treatment										
Age (years)										
All-cause mortality										
< 30		45	6123	0.73	1 (ref)	**< 0.0001**	1 (ref)	**< 0.0001**	1 (ref)	**< 0.0001**
30–39		114	12 401	0.92	1.25 (0.89–1.77)		1.33 (0.94 to 1.89)		1.04 (0.80 to 1.33)	
40–49		149	7527	1.98	2.69 (1.93–3.76)		2.69 (1.89 to 3.83)		1.92 (1.50 to 2.46)	
50+		279	4359	6.40	8.71 (6.36–11.93)		5.57 (3.90 to 7.95)		4.69 (3.70 to 5.95)	
< 30	Methadone	33	4998	0.66	1 (ref)	**< 0.0001**	1 (ref)	**< 0.0001**	1 (ref)	**< 0.0001**
	Buprenorphine	12	1125	1.07	1.62 (0.83–3.13)	0.1548	1.40 (0.72 to 2.73)	0.3243	1.58 (1.04 to 2.39)	0.0327
30–39	Methadone	98	10 049	0.98	1 (ref)		1 (ref)		1 (ref)	
	Buprenorphine	16	2353	0.68	0.70 (0.41–1.18)	0.1812	0.58 (0.34 to 0.99)	0.0450	0.50 (0.37 to 0.69)	< 0.0001
40–49	Methadone	131	5647	2.32	1 (ref)		1 (ref)		1 (ref)	
	Buprenorphine	18	1880	0.96	0.41 (0.25–0.68)	0.0004	0.25 (0.15 to 0.41)	< 0.0001	0.24 (0.18 to 0.32)	< 0.0001
50+	Methadone	244	2126	11.48	1 (ref)		1 (ref)		1 (ref)	
	Buprenorphine	35	2233	1.57	0.14 (0.10–0.19)	< 0.0001	0.07 (0.05 to 0.10)	< 0.0001	0.07 (0.05 to 0.09)	< 0.0001
Drug-related poisoning										
< 30		18	3321	0.54	1 (ref)	**0.8554**	1 (ref)	**0.7000**	1 (ref)	**0.3787**
30–39		38	6507	0.58	1.08 (0.61–1.89)		1.17 (0.65 to 2.11)		0.90 (0.60 to 1.34)	
40–49		20	4109	0.49	0.90 (0.47–1.70)		0.97 (0.48 to 1.96)		0.69 (0.43 to 1.12)	
50+		11	2426	0.45	0.84 (0.40–1.77)		0.76 (0.32 to 1.84)		0.69 (0.39 to 1.21)	
< 30	Methadone	13	2533	0.51	1 (ref)	**0.1506**	1 (ref)	**0.0507**	1 (ref)	**0.0024**
	Buprenorphine	5	787	0.64	1.24 (0.44–3.47)	0.6853	1.49 (0.51 to 4.36)	0.4622	1.92 (0.99 to 3.72)	0.0532
30–39	Methadone	30	4966	0.60	1 (ref)		1 (ref)		1 (ref)	
	Buprenorphine	8	1541	0.52	0.86 (0.39–1.87)	0.7036	0.78 (0.36 to 1.73)	0.5449	0.77 (0.48 to 1.23)	0.2759
40–49	Methadone	15	2874	0.52	1 (ref)		1 (ref)		1 (ref)	
	Buprenorphine	5	1236	0.40	0.78 (0.28–2.13)	0.6221	0.64 (0.23 to 1.77)	0.3870	0.66 (0.34 to 1.31)	0.2355
50+	Methadone	10	1113	0.90	1 (ref)		1 (ref)		1 (ref)	
	Buprenorphine	1	1314	0.08	0.08 (0.01–0.66)	0.0186	0.06 (0.01 to 0.44)	0.0060	0.08 (0.02 to 0.41)	0.0026

(*Continues*)

Table 3. (Continued)

	OST type	Deaths	PY	MR	Unadjusted		Adjusted[a]		IPW adjusted[a]	
					IRR (95% CI)	P	IRR (95% CI)	P	IRR (95% CI)	P
Comorbidity × treatment type										
Comorbidity										
All-cause mortality										
0		189	21 437	0.88	1 (ref)	**< 0.0001**	1 (ref)	**< 0.0001**	1 (ref)	**< 0.0001**
1		91	7045	1.29	1.47 (1.14–1.88)		1.41 (1.10 to 1.82)		1.23 (1.03 to 1.46)	
2+		307	1928	15.92	18.06 (15.07–21.65)		11.40 (9.23 to 14.08)		10.43 (9.10 to 11.96)	
0	Methadone	152	16 566	0.92	1 (ref)	**< 0.0001**	1 (ref)	**< 0.0001**	1 (ref)	**< 0.0001**
	Buprenorphine	37	4872	0.76	0.83 (0.58–1.19)	0.3022	0.46 (0.32 to 0.67)	< 0.0001	0.61 (0.49 to 0.74)	< 0.0001
1	Methadone	77	5209	1.48	1 (ref)		1 (ref)		1 (ref)	
	Buprenorphine	14	1836	0.76	0.52 (0.29–0.91)	0.0227	0.25 (0.14 to 0.44)	< 0.0001	0.28 (0.19 to 0.40)	< 0.0001
2+	Methadone	277	1045	26.50	1 (ref)		1 (ref)		1 (ref)	
	Buprenorphine	30	883	3.40	0.13 (0.09–0.19)	< 0.0001	0.07 (0.05 to 0.10)	< 0.0001	0.06 (0.04 to 0.08)	< 0.0001
Drug-related poisoning										
0		53	11 533	0.46	1 (ref)	**0.0110**	1 (ref)	**0.0009**	1 (ref)	**0.0122**
1		23	3941	0.58	1.27 (0.78– 2.07)		1.52 (0.93 to 2.48)		1.23 (0.86 to 1.75)	
2+		11	889	1.24	2.69 (1.41–5.16)		3.80 (1.86 to 7.75)		2.22 (1.30 to 3.79)	
0	Methadone	39	8307	0.47	1 (ref)	**0.0884**	1 (ref)	**0.0671**	1 (ref)	**0.0006**
	Buprenorphine	14	3227	0.43	0.92 (0.50– 1.70)	0.8002	0.94 (0.50 to 1.76)	0.8456	1.15 (0.79 to 1.67)	0.4710
1	Methadone	20	2779	0.72	1 (ref)		1 (ref)		1 (ref)	
	Buprenorphine	3	1162	0.26	0.36 (0.11– 1.21)	0.0978	0.33 (0.10 to 1.14)	0.0798	0.41 (0.20 to 0.82)	0.0117
2+	Methadone	9	400	2.25	1 (ref)		1 (ref)		1 (ref)	
	Buprenorphine	2	489	0.41	0.18 (0.04–0.84)	0.0292	0.17 (0.04 to 0.81)	0.0257	0.16 (0.05 to 0.50)	0.0016

IPW = inverse probability weighting based upon propensity scores; PY = person-years follow-up (person-years at risk); MR = mortality rate (deaths/100 person-years); IRR = incidence rate ratio; CI = confidence interval. Main effect and interaction *P*-values (2 degrees of freedom) are shown in bold type. [a]Adjusted for treatment period, age, gender, year, region and, where applicable, comorbidity and OST type.

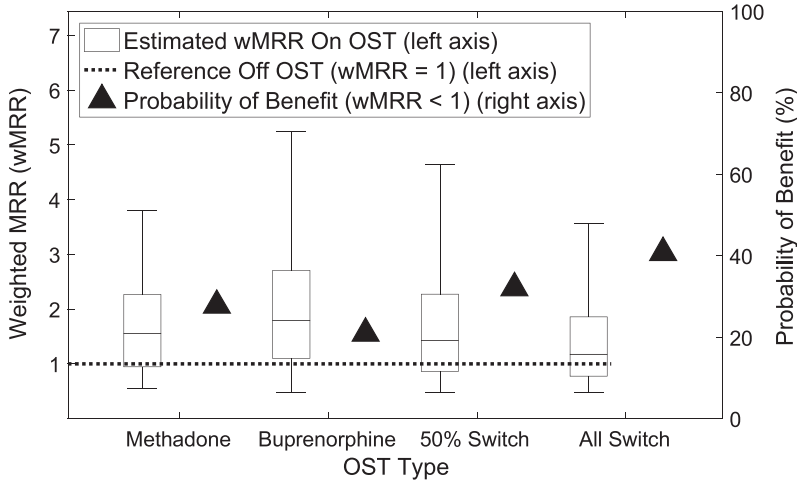

Figure 3 Estimated weighted mortality risk ratios (wMRR) and corresponding probability of benefit. A weighted mortality risk ratio (wMRR) compares drug-related poisoning mortality risk for patients on opioid substitution treatment (OST) (based on the observed mortality risks and duration of treatment shown in Table 1) and a hypothetical population of people who did not enter OST. A wMRR of 1 suggests that there is no difference in the number of drug-related poisonings in the population for people on OST (with wMRR < 1 and > 1 suggesting survival improved or worsened and lower or higher number of deaths in the population, respectively) compared to people not receiving OST. The wMRR also models the impact of inducing all patients on buprenorphine then switching either 50 or 100% patients to methadone (given observed duration of treatment)

Figure 4 shows that to reduce DRP by 25% by increasing OST duration alone would require a minimum median duration of 202 days for buprenorphine and 387 days for methadone: at 50% probability of success.

DISCUSSION

Main findings

We find consistent evidence that buprenorphine is associated with lower ACM and DRP mortality compared to methadone during the first 4 weeks and during the remaining time in treatment. We raise the hypothesis that buprenorphine has a greater effect on reducing mortality risk compared to methadone for older and more comorbid patients. However, in UK primary care the majority of patients receive comparatively short durations of treatment. Patients prescribed buprenorphine had a substantially lower average treatment duration than patients prescribed methadone. The combination of short average treatment durations and high mortality risk in the period after

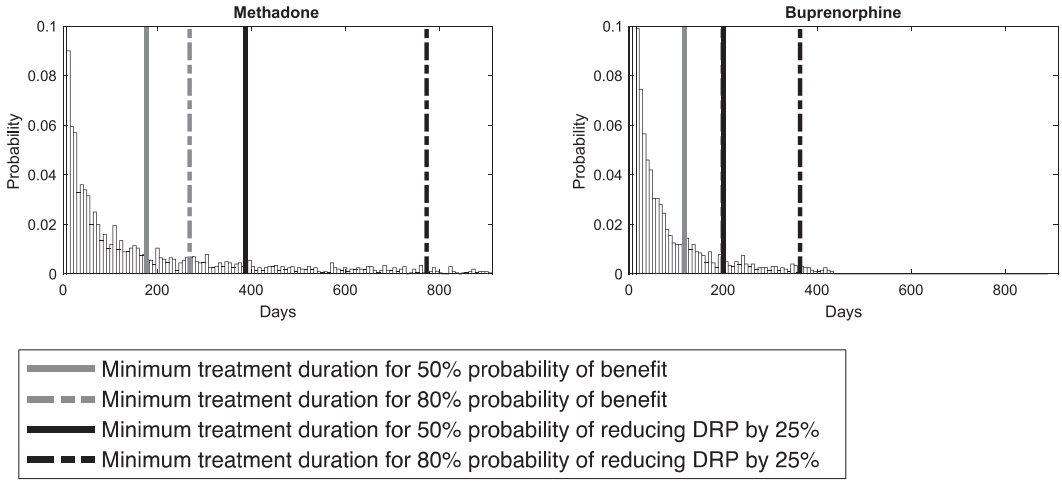

Figure 4 Length of treatment for patients on methadone or buprenorphine for opioid substitution treatment (OST) in primary care and estimated minimum duration to achieve positive benefit or a 25% reduction in drug-related poisonings (DRP). The figures show the distribution of OST duration and estimated minimum treatment duration required to have a 50 or 80% chance of achieving a positive benefit and a 25% reduction in DRP deaths compared to not being on OST. Probability that OST patients benefit (equivalent to wMRR < 1), or have a reduced risk of DRP by 25% (equivalent to wMRR < 0.75), is determined by the proportion of samples that have weighted MRR below the corresponding threshold (see Supporting information, Appendix S2)

treatment cessation suggests that in the United Kingdom neither buprenorphine or methadone are reducing the number of DRPs in the population.

Strengths and limitations

Observational cohorts present the best evidence, as trials are too underpowered to investigate differences in mortality risk in patients on OST [11,43,50]. Nonetheless, we acknowledge several limitations. First, there were differences in the distribution of confounders between patients prescribed buprenorphine or methadone. However, using propensity scores to adjust for this uneven distribution of confounders strengthened the intervention effect of buprenorphine compared to methadone for reducing DRP during the first 4 weeks of treatment and during the other time-periods. The presence of differences in mortality risks between patients prescribed methadone or buprenorphine more than 4 weeks after treatment ceased implies residual confounding. It has been argued that patients prescribed buprenorphine may be less severely addicted and more likely to recover than those prescribed methadone. However, in our study we found that older and more comorbid patients were more likely to be prescribed buprenorphine, and by the last calendar period (2010–14) more than 40% of patients were prescribed buprenorphine. We included information on self-harm, previous overdose, alcohol use, prison history and homelessness in propensity-score adjustments, and crucially we found no evidence of a difference in DRP during the first 4 weeks after leaving treatment, when one would expect any difference in relapse rates between patients on methadone and buprenorphine to have the greatest influence. Unfortunately, it is a common problem that large drug treatment cohorts lack refined measures on addiction severity and patient or clinical perceptions and preferences on OST modality [22,24,43].

Secondly, our efforts to exclude patients prescribed buprenorphine or methadone for pain relief (based on the type of formulation, clinical diagnoses/indications and minimum dose) may not have been entirely successful. However, if there was misclassification of OST episodes we believe it was more likely to affect patients on buprenorphine than methadone, as the former is used more often for other indications than opioid dependence. However, the mortality rates and patterns in DRP in and out of treatment are also consistent with other cohorts, and the same differential patterns of overdose by period were seen in our data set after excluding comorbid treatment episodes.

Thirdly, data on DRP were only available on half the cohort, which did not add bias, because the reasons (only available from GPs in England) were unrelated to future mortality risk but reduced power. Fourthly, we did not pre-specify testing the interaction between age and comorbidity and OST type, and need to be cautious on the interpretation both until replicated in other epidemiological studies and tested in pharmacological and clinical studies. Fifthly, there is no information on the reason for treatment cessation, so we assumed that patients dropped out of treatment if there was no tapering in the prescription dose during the last month of treatment. We found no evidence that the shorter duration for patients on buprenorphine was due to planned discharge. Sixthly, our estimates of the minimum duration required to achieve benefit do not take account of any other interventions that could reduce mortality risk. Finally, we are unable to compare whether patients seen in UK primary care are more or less comorbid than patients in other community drug services.

Other evidence and implications

A recent systematic review concluded that OST reduces mortality rates but could not make any direct or definitive conclusions when comparing methadone and buprenorphine [43]. The review reported greater reductions in mortality risk between in and out of OST for patients prescribed methadone but lower overall mortality rates in both periods for patients prescribed buprenorphine.

We observed an ageing and increasingly comorbid population of opioid-dependent patients with comparatively high rates of ACM, although consistent with other cohorts and the increase in drug-related deaths in the UK population [43,51]. Forensic data also suggest substantial comorbidity in people dying of an opioid overdose, and it has been hypothesized that systemic illnesses may compromise physiological and pharmacological responses to opioid action on respiratory depression and opioid metabolism, thereby increasing overdose risk [52,53]. A study in Scotland suggested that mortality risk increased with age in methadone patients [54], although neither study can test the mechanism of any increased risk.

Our findings are consistent with evidence from New South Wales (NSW), Australia that showed a substantially reduced risk of DRP in the first 4 weeks of treatment for patients on buprenorphine compared to methadone, the scale of which is unlikely to be reversed through introducing additional unmeasured confounders [24]. However, the NSW data did not observe the larger differences for all-cause mortality and was unable to adjust for confounders which, in our study, tended to strengthen differential effects [21].

Our data also align with trial and other observational data suggesting that patients are less likely to be retained on buprenorphine treatment compared to methadone (i.e. that treatment duration is shorter) [19,34,37]. Long-

term follow-up of trial participants reported no differences in drug outcomes for patients randomized to buprenorphine or methadone, but was underpowered to detect differences in mortality [55].

Previously we highlighted that treatment duration could be critical to preventing drug-related deaths in the population [20]. The majority of drug-related deaths are among individuals not in treatment [22,56]. Restricting access to OST is associated with high rates of mortality among opioid-dependent people who have been discharged or denied treatment [57]. Open access to OST is a feature of the 'British System' of drug treatment and a response to HIV/AIDS epidemic in the early 1990s [58]. Coverage and duration of OST is also critical to the prevention of HIV and HCV in opioid-dependent people who inject drugs [59,60]. However, our new analyses show that OST duration seems to follow an exponential decay, with the majority of patients having comparatively short treatments and not receiving maintenance therapy as intended, with prolonged duration of treatment and planned tapered discharge. Nosyk *et al.* has also shown in British Columbia that the majority of patients do not discharge successfully from maintenance therapy [61], but a recent study in multiple sites suggests that the preponderance of shorter treatments may be greater in the United Kingdom than elsewhere [62]. For example, a study in Germany found almost two-thirds of patients retained on OST at 1 year [63,64].

At a population level our findings generate conflicting pictures. Mortality risk is reduced during treatment, as shown in reviews that compare mortality rates in and out of OST [43], but our model estimates suggest that the overall treatment duration, at least in UK primary care, is too short to have a population benefit. Moreover, the reduction in risk at treatment cessation for patients on buprenorphine may be outweighed by less overall protection as a result of the short and skewed distribution in duration of treatment. Our models also suggest that in the United Kingdom a potential 'quick fix', as suggested in earlier reports, of inducing all OST patients on buprenorphine and then switching patients to methadone, is unlikely to lead to a substantial reduction in drug-related poisonings in the population unless overall duration of treatment is extended [24]. Other large-scale epidemiological studies are needed in order to strengthen the evidence and replicate and test our findings, but interventions to improve OST retention also are needed. Rather than compare OST modalities against each other we need large trials in the United Kingdom and elsewhere that can test how best to stratify, combine and optimize OST alongside other behaviour change interventions [65], both to reduce mortality risk at induction and retain people in treatment long enough to reduce the number of drug-related deaths in the population.

Declaration of interests

J.M. declares investigator-led, educational grant funding from Indivior (administered by Action-on-Addiction) for a study of personalized psychosocial intervention for non-response to opioid agonist treatment (ARC trial), and support from NIHR (HTA) for a trial of extended-release naltrexone. He acknowledges part-time employment as Senior Academic Adviser for the Alcohol, Drugs and Tobacco Division, Health Improvement, Public Health England and consultancy for the US National Institute on Drug Abuse, Centre for Clinical Trials Network. In the past 3 years, he received honoraria from Merck Serono (2015; clinical oncology training); Martindale (2017; expert meeting on OUD); and Indivior (via PCM Scientific) as co-chair (2015, 2016) and chair (2017) for the conference on Improving Outcomes in Treatment of Opioid Dependence. L.M. declares grant funding for an investigator-led, educational grant from Indivior (administered by Action-on-Addiction) for the ARC Trial. He holds no stocks in any company. T.M. has received research funding from the UK National Treatment Agency for Substance Misuse, Public Health England, the Home Office and Change Grow Live, a third-sector provider of substance misuse services. He has been a member of the organizing committee for conferences supported by unrestricted educational grants from Reckitt Benckiser, Lundbeck, Martindale Pharma and Britannia Pharmaceuticals Ltd, for which he received no personal remuneration. He is a member of the UK Advisory Council on the Misuse of Drugs. J.S. is a clinician and researcher and has worked extensively with agencies in the addiction treatment fields and addiction-related charities and with government departments and has contributed to clinical guidelines on treatment types and provision. J. S.'s employer (King's College London) has received, connected to his work, project grant support and/or honoraria and/or consultancy payments from Department of Health, NTA (National Treatment Agency), PHE (Public Health England), Home Office, NICE (National Institute for Health and Clinical Excellence) and EMCDDA (European Monitoring Centre for Drugs and Drug Addiction) as well as research grants from (last 3 years) NIHR (National Institute on Health Research), MRC (Medical Research Council) and Pilgrim Trust. He has also worked with WHO (World Health Organization), UNODC (United Nations Office on Drugs and Crime), EMCDDA, FDA (US Food and Drug Administration) and NIDA (US National Institute on Drug Abuse) and also other international government agencies. J.S.'s employer (King's College London) has also received, connected to his work, research grant support and/or payment of honoraria, consultancy payments and expenses from pharmaceutical companies (including, past 3 years, Martindale, Indivior, MundiPharma, Braeburn/Camurus) and trial medication supply from iGen and Braeburn. J.

S.'s employer (King's College London) has registered intellectual property on an innovative buccal naloxone with which J.S. is involved, and J.S. has been named in a patent registration by a Pharma company as inventor of a potential concentrated naloxone nasal spray. For updated information see http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx. M.H. and P.V. acknowledge support from NIHR Health Protection Research Unit in Evaluation of Interventions and the NIHR School of Public Health Research. M.H. has received unrelated unrestricted honoraria from Gilead, Abbvie, Jansen and Merck Serono. No other disclosures by the other authors are reported.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1 Definition of drug-related deaths.
Table S2 Confounders and association with type of opioid substitution treatment and mortality risk.
Table S3 Duration of opioid substitution treatment (OST) in primary care and specialist drug agency.
Table S4 Unadjusted all-cause mortality rates and drug related poisonings rates and adjusted incidence rate ratios by opioid substitution treatment (OST) period and OST type comparing final sample (model A) with (model B) mortality rates excluding patients and episodes with evidence of comorbidity; (model C) mortality rates including episodes with multiple medications; (model D) additional adjustment for evidence of tapering of OST dose prior to discharge/cessation; and (model E) negative binomial model to account for potential dispersion in the data.
Appendix S1 Confounding.
Appendix S2 Comparing impact of opioid substitution treatment (OST) on morality due to drug-related poisonings (DRP) in the population.

